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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/079,834	05/15/1998	JOHN D. MOUNTZ	D6005	8770

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/079,834	MOUNTZ ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8,9 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8,9 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the applicant's supplemental appeal brief filed on 9/2/03, PROSECUTION IS HEREBY REOPENED. The new grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claims 1, 3-6, 8-9, and 16 are pending in the instant application.

Claim Rejections - 35 USC § 112

The rejection of claims 1, 3-6, 8-9, and 16 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn in view of new grounds of rejection set forth below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 8-9, and 16 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method of inducing systemic T-cell tolerance to an antigen in an individual in need of such treatment, comprising the step of : administering to said individual peritoneal macrophages which (1) express high levels of Fas ligand resulting from co-infection with AdLoxPFasL and axCANCre adenoviruses, (2) do not express Fas and (3) express said antigen, wherein said antigen presenting cells induce apoptosis of Fas-Positive T-cells directed towards said antigen resulting in said induction of systemic T-cell tolerance to said antigen.

;does not reasonably provide enablement for inducing systemic tolerance using antigen presenting cells other than fas-negative peritoneal macrophages, or for creating immune-privileged sites in an individual to decrease graft rejection by introducing fas positive or negative Fas-ligand expressing donor antigen presenting cells. It is further noted that the specification does not provide an enabling disclosure for delivering genes to inhibit apoptosis to antigen presenting cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not provide an enabling disclosure for using antigen presenting cells which are not fas negative peritoneal macrophages in the disclosed methods of inducing systemic tolerance to an antigen. This grounds of rejection applies to claims 1, 3-6, 8-9, and 16. Claims 1, 3-6, and 8-9 recite the administration of fas negative antigen presenting cells which express fas ligand and the antigen of interest. Claim 16 is broader than claims 1, 3-6, and 8-9 and

recite the administration of donor antigen presenting cells which express fas ligand and which may be fas positive or negative. The purpose of the methods of claims 1, 3-6, and 8-9 is also narrower in scope than the purpose of the method of claim 16. Claims 1, 3-6, and 8-9 recite a method inducing systemic tolerance wherein fas-positive T cells directed towards the antigen apoptose following administration of the fas-ligand expressing antigen presenting cells. In claim 16, the methods are directed to creating an immune privileged site capable of decreasing graft rejection. The specification and the declaratory evidence provided by the applicants present data obtained using fas-negative peritoneal macrophages which have been infected *ex vivo/in vitro* with the AdLoxPFasL and axCANCre adenoviruses. The working examples and declaratory evidence show that transplantation of these peritoneal macrophages can induce the apoptosis of the host T cells. However, while the specification broadly states that any antigen presenting cell expressing fas ligand can be used to induce T cell tolerance, the evidence of record only supports the use of fas-negative peritoneal macrophages. From the time of filing to the present, the role of fas ligand in inducing tolerance versus inflammation has been controversial. In a review of fas ligand which discusses a number of peer reviewed papers published at the time of filing between 1996 and 1998, Restifo discusses the fact that although the idea that fas ligand expression could grant immune privilege status rapidly gained popularity, substantial evidence to the contrary exists in the literature (Restifo (2000) Nature Med., Vol. 6 (5), 493-495). Numerous papers cited by Restifo document the fact that expression of recombinant fas ligand by many different cell types results in an inflammatory response *in vivo* rather than tolerance. Of specific note, Kang et al. demonstrated that islet cells, fibroblasts, epithelial cells, and various tumor cell lines genetically modified to express fas ligand are rapidly rejected *in vivo* as a result of a profound

inflammatory response (Kang et al. (1998) Transp. Proceed. Vol. 30, page 538). Seino et al. also showed that fas-negative baby hamster kidney cells and fas-negative T lymphoma cells transfected with cDNA encoding fas ligand stimulated a substantial inflammatory response and were rapidly rejected *in vivo* (Seino et al. (1997) Transp. Proceed., Vol. 29, 1092-1093). Based on the data as a whole, Restifo concludes that ectopic expression of fas ligand on cells results in inflammation not immunosuppression (Restifo, page 493-494). Thus, based on the cumulative data available at the time of filing, the skilled artisan would have expected inflammation and not immunosuppression after transplantation of cells which have been modified to express fas ligand. Therefore, applicant's data generated using fas-negative peritoneal macrophages cannot be extrapolated to other types of antigen presenting cells, since the prior art shows that other types of antigen presenting cells which express fas ligand cause inflammation and not tolerance. Thus, based on the evidence of record which is limited to fas negative peritoneal macrophages which express fas ligand, and the teachings of the prior art that most antigen presenting cells which express fas ligand induce inflammation and not tolerance *in vivo*, it would have required undue experimentation to practice the scope of the claims as written.

The specification does not provide an enabling disclosure for creating an immune-privileged site in an individual to decrease graft rejection by administering fas-positive or fas-negative fas-ligand expressing donor antigen presenting cells to the individual. This grounds of rejection applies to claim 16 only. As noted above, the prior art shows that while the idea that fas ligand expression can grant immune privilege, the actual experimental data presented in the literature demonstrates that ectopic fas ligand expression on transplanted cells causes inflammation and rejection, not immune privilege (see Restifo, Kang et al., and Seino et al.).

Further, the expression of fas on the transplanted cells can also cause apoptosis of the transplanted cell themselves (Zhang et al. (1998) J. Virol., Vol. 72 (3), 2484-2490,see page 2484, column1). In experiments which are analogous to applicant's experiments, Murave et al. teaches that transplantation of syngeneic pancreatic islets which express low levels of Fas and which have been transduced *ex vivo* with an adenovirus vector encoding Fas ligand rapidly lose function as a result of apoptosis and inflammatory immune responses (Murave et al. (1997) Human Gene Ther., Vol. 8, 955-963, page 960, column 2). Thus, based on the teachings of the art that expression of Fas Ligand in cells which already express Fas results in apoptosis of the transfected cell itself, the teachings of the prior art that the transplantation of cells expressing fas ligand does not grant immune privilege as the cells are rapidly rejected, the lack of evidence of record that the transplantation of any fas ligand expressing cell can result in immune privilege and a decrease in graft rejection, and the breadth of the claims, the skilled artisan would not have predicted success in promoting T cell tolerance or immune privilege to fas positive cells *in vivo* by transfecting the cells with an adenovirus encoding Fas Ligand. Thus, it would have required undue experimentation to practice the scope of the claim as written.

The specification does not provide an enabling disclosure for delivering a gene to inhibit apoptosis to transplanted antigen presenting cells *in vivo*. This grounds of rejection applies to claims 8 and 9 only. The claims are broad and read on the delivering a gene to inhibit apoptosis to the fas-ligand expressing antigen presenting cells *in vitro* or *in vivo*. While the specification is enabling for the *in vitro* delivery of a gene to inhibit apoptosis to antigen presenting cells, the specification fails to provide sufficient guidance for targeting delivery of a gene to transplanted antigen presenting cells *in vivo*. The specification does not provide any guidance as to targeted

vectors capable of specifically targeting and transfecting macrophages or any other type of antigen presenting cell *in vivo*. Further, at the time of filing , the skilled artisan did not consider the targeting of vectors to specific cell types *in vivo* to be predictable . Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). Therefore, in view of the art recognized unpredictability in achieving targeted gene delivery *in vivo* using vectors currently available at the time of filing, the absence of guidance provided by the specification for any of the conditions and parameters under which specific tissues or cells can be targeted *in vivo* following direct administration of a recombinant vector encoding a gene to inhibit apoptosis, the limitation of the working examples to the delivery of genes to antigen presenting cells *ex vivo/in vitro*, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to deliver a gene to a specific set of transplanted antigen presenting cells *in vivo* by the direct administration of any vector encoding the gene.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 contains grammatical errors which render the claim confusing. Specifically, in line 5 of claim 1, the claim recites, "...(1) express high level of fas ligand resulted from co-infection..." . Amendment of the claim to recite, "...(1) express high levels of fas ligand result**ing** from co-infection...", would overcome this rejection.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER